ETS Health Effects

Children

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WSA ETS (children) consensus (DRAFT -

Objective

- To understand the potential impact of ETS on child health which will provide necessary information to determine the best approaches to minimising such effects.
- Where appropriate recommendations for further research are determined

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WSA ETS (children) consensus (DRAFT -

Overview

- Reviews information relating ETS exposure during childhood to potential health effects
- Does NOT specifically review potential effects of maternal smoking during pregnancy
- Conclusions / Recommendations

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Definitions

- ETS - Environmental Tobacco Smoke
  - Highly diluted mixture of aged sidestream smoke and exhaled mainstream smoke
- Children - as defined in Medline:
  - All children: 0-18 years
  - Newborn: 0-1 month
  - Infant: 0-23 months
  - Preschool: 2-5 years
  - Child: 6-12 years
  - Adolescent: 13-18 years
- Health Effects - see slide 10
- *in utero* exposure -
  - Maternal smoking during pregnancy
  - Excludes ETS exposure of non-smoking pregnant women

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Consensus Review Structure:

- Relies largely on informed analysis of reports from public health and/or government organisations
- Covers major endpoints according to most frequently reported categorisation (i.e. as presented by these reports)
- Draws conclusions based on available evidence (full Bradford-Hill analyses have not been performed)

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Note: It has been suggested that, to be consistent with the ETS (adult) consensus, (and the causation consensus) we should review each endpoint in consideration of the Bradford Hill aspects.

Note: For almost all endpoints reviewed it is fairly straightforward to summarise evidence with respect to temporality.

• Assessment of the strength of the associations is often difficult. Although in general these associations are fairly weak there are specific subgroups for many endpoints which suggest stronger relationships - although the attribution of this to ETS exposure is often unclear.

• Without a full analysis of heterogeneity consistency is difficult to completely assess. For all of the endpoints discussed here such an analysis has not been conducted.

• Specificity, per se, can also be addressed, but since the original proposal of Bradford Hill is generally less informative than first thought!

•There is evidence on biological gradient for many of the endpoints, but it is dubious in most cases since the assessment of exposure (as described in the next slide) does not lend itself to accurate assessment of dose.

•Discussions so far on plausibility suggest that evidence such as effects on BHR or lung-function differences in exposed and unexposed subjects may be considered as evidence for a plausibility

•Coherence could be considered as evidence suggesting mechanisms through which ETS could cause the effect in question. However this has only rarely been addressed, and almost entirely based upon speculation without any data to support it.

•Experiment would refer to animal experiments. So far, these have not been included specifically in this review.

•There is little, if any, information on analogy to support the evidence reviewed. Perhaps the most commonly cited is air pollution (e.g. suggested as an adjuvant for infectious diseases) - although arguably the evidence for air pollution is not sufficiently strong to support an analogy argument for ETS?

In conclusion a full Bradford-Hill type analysis cannot be effectively performed in the absence of more data. Much of this data should be acquired from the further research proposed by this consensus group, or already underway through PM WSA projects

Barriers to Assessing the Literature

- Extensive literature (~300 articles/year)
- Endpoints are often poorly defined and vary among studies
- Varied study designs
- Confounders (*in utero* exposure)
- Age-dependent effects and/or associations are apparent
- Limited discussion of criteria for causal inference

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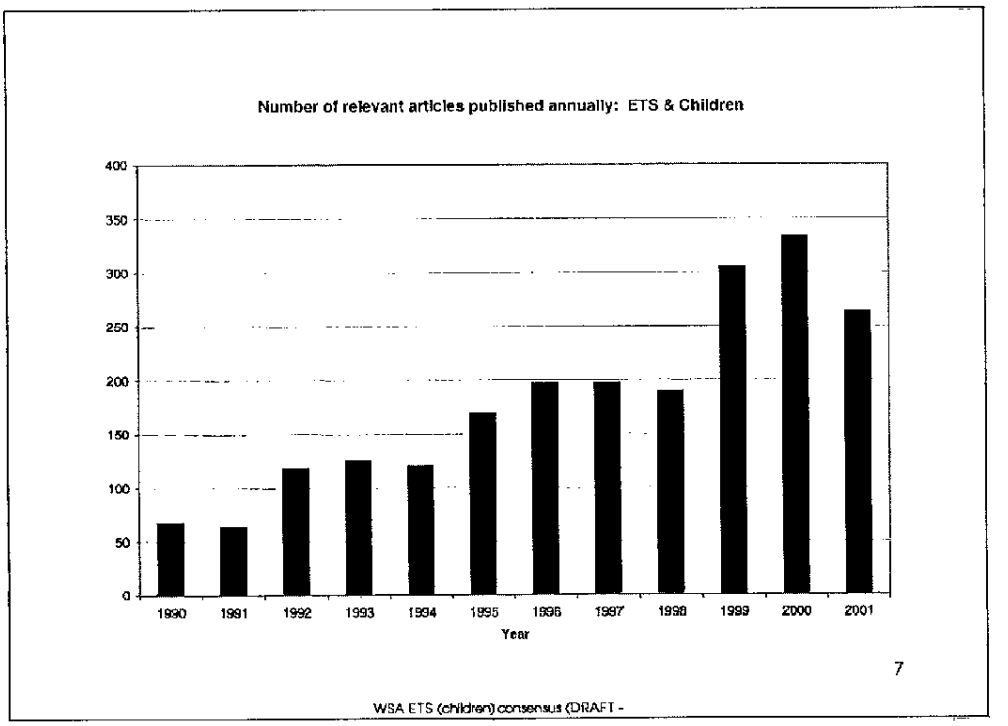
Note: A common feature of the findings from studies on potential effects of ETS on childrens health is that effects are often reported as being more pronounced in infants and pre-school children. Although specific age definitions for these age groups may differ, and thus studies may look at different age-group definitions, this trend towards more pronounced effects at the younger ages can generally be seen. As indicator definitions only, the Medline age distributions provided as follows may be useful:

All Children:	0-18 years
Newborn:	0-1 month
Infant:	0-23 months
Preschool:	2-5 years
Child:	6-12 years
Adolescent:	13-18 years

Note: As for other types of epidemiological survey, confounding always may play more or less of a role in the observed associations. Particular attention has to be paid to the potential role of confounding from exposure *in utero* in these studies as they generally use maternal smoking as their measure of exposure, which is clearly very closely associated with maternal smoking during pregnancy and thus exposure to the unborn child via this route.



Note: figures calculated from comparing a medline search (tobacco+smoke+pollution and child*) with the articles collected and stored in our own Documentum database. This provided the following measures per year:

1. Total number of articles in medline satisfying search criteria
2. %ge of "relevant" articles in medline per year (based on screening of abstracts for first 20 medline hits)
3. Total number of articles in our literature collection per year (based on documentum search)
4. Estimate of proportion of articles "missed" by medline, or "missed" by our own collection.

Note: This original estimation was performed early in 2000. A reevaluation to update the figure through 2001 indicates that the level of publication activity in this area remains high.

Official Reports

- US Surgeon General - 1986
- US EPA - 1992
- California EPA - 1997
- Australian NH&MRC - 1997
- SCOTH - 1998
- WHO - 1999

Note: Other reviews for specific endpoints are included where the contribution are considered informative (e.g. PM commissioned reviews or committee review of a specific endpoint)

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Common characteristics of these reports:

Consensus review (by committee / groups of scientists)

Involve independent review of individual studies

Public health or governmental status

Multiple endpoints reviewed (though not necessarily the same for each report!)

Full Reference:

US DHHS 1986 " The Health Consequences of Involuntary Smoking" a report of the Surgeon General

US EPA 1992 " Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders"

California EPA 1997 Office of Environmental Health Hazard Assessment "Health Effects of Exposure to Environmental Tobacco Smoke: Final Report, September 1997"

Australian National Health and Medical Research Council 1997 "The Health Effects of Passive Smoking: A Scientific Information Paper, November 1997"

Poswillo, David (Chariman) 1998 "Report of the Scientific Committee on Tobacco and Health" UK DoH, Northern Ireland DHSS, The Scottish Office DoH, Welsh Office

WHO 1999 "Tobacco Free Initiative: International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. 11-14 January 1999, Geneva, Switzerland.

Exposure Metrics

- Questionnaire-derived information*
  - Parental (Maternal / Paternal)
  - Other household members
  - Number of cigarettes smoked in presence of child
  - "Quantitative" estimates of ETS levels (e.g. high/medium/low)
  - Hours of exposure to ETS
- Air-monitoring (area and personal)
- Biomarkers of exposure

* The majority (~90%) of articles report on studies using questionnaire-derived information

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This is not a comprehensive list of the different exposure metrics that have been used. For example some papers have reported differentiation between smoking household and non-smoking household. Others have also looked at smoking in day-care centres as a source of exposure etc. The main point is to illustrate the most common parameters used. Several reviewers have also noted that there is a need for studies which can more clearly define exposure.

It should also be noted that there is no "gold standard" for exposure measurement of ETS, and in all probability it will never be truly possible to determine one.

Note: As a rough assessment of the proportion of articles reporting on studies using questionnaires as the measure of exposure we looked at the distribution presented in the tables of the NHMRC report (selected purely arbitrarily because it was the nearest to hand!) From Tables 3.7; 3.8; 3.9; 3.13 and 3.14 the distribution of questionnaire based studies to other measures of exposure was: 5:1 / 18:2 / 13:5 / 7:7 / 45:3.

Most frequently reported health effects:

- **Respiratory Effects**
- **Otitis Media (Middle Ear Disease)**
- **SIDS (Sudden Infant Death Syndrome)**
- **Childhood Cancers**
- **Childhood Infections**
- **Neuro-developmental / Behavioural Difficulties**

Respiratory Effects:

- Asthma
- Bronchial Hyper-responsiveness
- Lower Respiratory Illness
- Lung Function
- Respiratory Symptoms

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Respiratory Effects: Asthma

- Major reviews covering this subject:
  - US Surgeon General - 1986
  - US EPA - 1992
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - SCOTH - 1998
  - WHO - 1999
- Additional review specifically on Asthma:
  - IOM - 2000

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Note: IOM (2000) "Clearing the Air: Asthma and Indoor Air" National Academy Press

Respiratory Effects: Asthma

- Epidemiological studies on asthma include:
  - Asthma development
  - Exacerbation of asthmatic symptoms

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Respiratory Effects: Asthma

- Diagnostic endpoints may include:
  - parental report
  - physician's diagnosis
  - "wheezy" illness
  - satisfying specific diagnostic criteria
    - bronchial hyper-responsiveness
    - atopy (indications of allergic tendency)

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Note: Atopy can be defined as .. "The propensity to produce IgE antibody to allergens that are commonly encountered in the general environment" See A.J. Newman Taylor "ABC of Allergies", BMJ 1998, 316: 997-999.

For a large number of studies potential atopic status is assessed by reference to other allergic manifestations (allergic rhinitis or excema), history of atopy in first degree relatives, high circulating IgE levels, or even skin prick tests)

Wheeze and Asthma:

"The description of wheezing illness in preschool children has always been confused. Terms such as wheezy bronchitis, wheeze associated respiratory illness, and asthmatoid bronchitis have been used in the past to describe episodic wheeze in infants and young children. These terms arose because it was felt by paediatricians that episodic wheeze in this age group had a more benign prognosis than asthma of older children. More recently, the term asthma has been advocated to describe all wheezing illness in children, allowing no distinction between virus induced wheeze and other varieties of asthma."

Wilson, 1989 (Arch. Dis Child, 64: 1194-1199)

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Note: A trend appears to be occurring in scientific congresses on this subject whereby more emphasis is being laid on the importance of fully characterising various disease sub-types of Asthma.

Respiratory Effects:Asthma IOM 2000

"Common problems frustrated our efforts, starting with the imprecise and variable definition of asthma used in research studies and followed immediately by what it means to "cause" asthma." ..... "Exposure to some environmental factor or factors is required to elicit the clinical expression of asthma, i.e., cause the development of asthma. The same or other agents may then cause exacerbation of asthma symptoms in these individuals. Thus, the committee divided its analysis into whether an agent might cause asthma development or exacerbation of symptoms."

"Clearing the Air; Asthma & Indoor Air Exposures" IOM, 2000

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Respiratory Effects: Asthma US SG 1986

- 7 studies reviewed on asthma or bronchial responsiveness associated with ETS exposure
- Evidence regarding causality
  - suggestive for asthma exacerbation due to maternal smoking
  - insufficient / inconclusive for asthma development
- Conclude that further research required

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Note: See p55-58; considers bronchial hyper-responsiveness and Asthma together. Studies reviewed:

Gortmaker et al, 1982 - Asthma & Severe Asthma RRs 1.5-1.8; 2.0-2.4

Schenker et al, 1983 - No relationship with parental smoking

Horwood et al, 1983 - No relationship with parental smoking

Murray & Morrison, 1986 - mothers but not fathers

The remaining studies seem chiefly to be looking at BHR....

Note difficult to represent magnitude - RR only given for Gortmaker....

Also note p58 " Furthermore the complex interrelationships among respiratory illness, atopy, parental smoking and airway responsiveness have not been clarified and require further study."(As above)

Respiratory Effects: Asthma US EPA 1992

- additional 10 studies reviewed
- evidence regarding causality:
  - sufficient for asthma exacerbation
  - "risk factor" for asthma development but evidence not conclusive for causality
  - noted that "..levels of exposure required to induce asthma in children are high"

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EPA p7-50 "A simple bronchospastic effect of cigarette smoke is probably not responsible for the increased severity of symptoms associated with passive smoking because acute exposure to ETS has been found to have little immediate effect on lung function parameters and airway responsiveness in asthmatic children...."

Note RRs reported in table 7-7 range from no-effect through to 9.0 (95%CI 2.4-34.0) for one study! Next largest RR is 3.1. These are not specifically separated out in support of induction of new cases or exacerbation of old. Discussion from p. 7-51 on induction...

EPA p 7-51: "New evidence available since the SG's report and the NRC report also indicates that passive smoke exposure increases the number of new cases of asthma among children who have not had previous episodes." ..... "In fact, concordance in the relationship between ETS exposure and both questionnaires and objective parameters such as lung function or bronchial provocation tests has been reported in several studies. The association is also biologically plausible; the mechanisms that are likely to be involved in the relationship between ETS exposure and asthma have been discussed extensively in Section 7.2. The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive."

Respiratory Effects: Asthma California EPA - 1997

- reviewed 15 studies on exacerbation
- performed meta-analysis of 31 studies on asthma development
- evidence re causality
  - sufficient for asthma exacerbation
  - "consistent and compelling" for asthma development
    - pooled RR 1.44 (95% CI = 1.27-1.64)
- strongest association with ETS exposure from the mother
- stronger associations noted in younger children

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Note: CAL-EPA meta.-analysis for asthma development appears to select the highest ORs reported in many of the individual papers included. This may be a fairly biased estimate of the true pooled result.

Also note CAL-EPA reviews the evidence for asthma induction (development) with respect to B-H aspects...p6-37 - 6-41

Strength - Yes (statistically significant; 14/37 with Ors >2.0)

Consistent - Yes (consistent despite diversity of study designs)

Dose-response - Yes, "simple biological gradient"(effect only observed for mothers smoking >10 cigs per day)

Temporality - Yes

Coherence - Yes (adult active and passive smokers - i.e. analogy?)

Biological plausibility - Yes (strong) (increased risk of respiratory infections; airway hyperresponsiveness; possible increase in risk of atopy; active smoking causes airway inflammation)

Specificity considered obsolete; analogy and experiment considered superfluous in this instance

"Taken as a whole, the epidemiologic evidence of causation is compelling"

Respiratory Effects: Asthma NH&MRC - 1997

- 48 studies reviewed
- evidence re causality:
  - sufficient for asthma exacerbation
  - sufficient for asthma development
- association strongest for:
  - ETS exposure from the mother
  - older children
- contribution from *in utero* exposure probable
- roughly a 30-80% increase in asthma symptoms in most studies

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See p 28 - NHMRC reviews evidence in terms of B-H aspects..

See p 2 "48 studies.."

Strength - "moderate" - "unlikely to be due to chance"

Dose-response - relatively few studies, but some evidence is available from both questionnaire data and cotinine measurements - "some evidence that the strength of the association between ETS and asthma symptoms is greater for older children, which may be a consequence of cumulative, prolonged exposure.

Consistency - general consistency

Specificity - No (but not generally considered important)

p48 -Temporal - Yes

Biological Plausibility - Yes (potential mechanisms = increased airway sensitivity; increased Atopy)

Analogy - Yes - (active smoking)

No specific discussion of coherence, or experiment

Respiratory Effects: Asthma SCOTH 1998

- based on a commissioned review of ~50 articles
- evidence re causality:
  - sufficient for asthma exacerbation
  - convincing for prevalence (development)
    - pooled RR 1.17 (95%CI 1.10-1.25, n=14) for either parent smoking
    - RR based on 4 cross-sectional studies for both parents smoking 1.52 (95% CI 1.34-1.72)
  - unlikely to be related to "underlying asthma tendency"
- association strongest for:
  - ETS exposure from the mother
  - younger children
- contribution from *in utero* exposure probable

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See p109

Note - SCOTH reviewed "asthma and respiratory symptoms" together!

It is difficult to determine exactly how many studies could be counted as being "reviewed" The table on p109 lists 43+3 reviewed on respiratory symptoms; 52+2 on asthma incidence etc

Numerous meta-analyses were reported on p110. Ranging from 1.13(1.04-1.22) for Asthma incidence in children >6yrs old whose mother smoked (based on 4 studies) to 1.52(1.34-1.72) for Asthma prevalence with both parents smoking (based on 7 studies)

Note from Annex I, p107 "We thus face a contradiction. Longitudinal studies demonstrate that maternal smoking is associated with an increased incidence of wheezing illness, particularly at younger ages. This excess incidence of early wheezing illness appears to be largely non-atopic "wheezy bronchitis" and to run a relatively benign course. However, amongst children with established asthma, parental smoking is associated with more severe disease. We believe that this paradox is explained by viewing ETS as a trigger of wheezing attacks (probably acting in conjunction with infection), rather than a cause of the underlying asthma tendency." Our interpretation is supported by the lack of a positive association between ETS and atopic sensitisation..."

Respiratory Effects: Asthma WHO 1999

- group asthma and respiratory symptoms together
- >60 studies reviewed
- evidence re causality:
  - sufficient for asthma exacerbations
  - "probably does not cause the underlying asthma trait"
- association strongest for:
  - ETS exposure from the mother
  - younger children

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Note: The above is based on the final "Consultation Report". We note, however, that in Samet's Synthesis document, prepared for discussion at the consultation meeting it is stated that.. "As evidence has mounted it has become clear that ETS exposure is also a cause of childhood asthma."

This apparent inconsistency is indicative of the complicated nature of interpretation of these study findings.

Respiratory Effects: Asthma IOM 2000

- based on Cook and Strachan, 1999
- evidence re causality:
  - sufficient for asthma exacerbation in preschool children, but limited for older children
  - sufficient for asthma development in "younger" children (mainly due to *in utero* exposure)
  - inadequate for asthma development in older children

Cook and Strachan, (1999) Thorax 54(4): 357-366

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Respiratory Effects: Asthma Exacerbation

- Based on our review it was our opinion that all these reports concur that there is a causal association between ETS exposure and exacerbation of asthma in childhood

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Respiratory Effects: Asthma Development

- 2 reviews conclude evidence is inconclusive
  - US SG 1986, US EPA 1992
- 2 reviews conclude evidence is sufficient
  - CAL EPA 1997, NHMRC 1997
- 2 reviews conclude evidence is sufficient, but ETS exposure is not related to "underlying trait"
  - SCOTH 1998, WHO 1999
- 1 review concludes evidence sufficient for younger children only, mostly due to *in utero* exposure
  - IOM 2000
- SCOTH 1998, WHO 1999 & IOM 2000 based on same source review (Cook & Strachan, 1999)

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WSA ETS (children) consensus (DRAFT -

Note: CAL-EPA appear to have performed a meta-analysis which has selected out some of the higher RRs in individual studies without any obvious justification for doing so. The NHMRC based their conclusions on the median value of 50 estimates of relative risks - no formal meta-analysis appears to have been applied.

WHO, SCOTH and IOM however, appear to have based their conclusions on comprehensive reviews and meta-analyses. In fact the WHO is based on an updated version of the same meta-analysis considered by SCOTH.

Note 08.05.02 Note the citation for the source review is not obvious ... there were many articles published from the group reviewing the data. The one cited is the last "summary and update" ....(Cook and Strachan, 1999, Thorax, 54: 357-366)

Respiratory Effects: Asthma - WSA Consensus

- Asthma exacerbation:

  We are in agreement with the PH reports on this endpoint:

  – The effect is more pronounced in "younger" children

  – The evidence is consistent with a causal association

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WSA ETS (children) consensus (DRAFT -

Note: The term "younger" has been used here as it is impossible to define the age groups referred to. There are many different study designs which split the ages into different groups. The general trend is towards more pronounced effects at earlier ages, but it would be misleading to identify a particular age group at which this effect is observed.

Respiratory Effects: Asthma - WSA Consensus

- Asthma development:
  - two meta-analyses (CAL-EPA 1997, Strachan and Cook, 1998) determined statistically significant, albeit weak associations
  - review of these meta-analyses shows considerable heterogeneity
  - there are differences between the major reports in conclusions drawn from these same meta-analyses
  - WSA is currently performing our own meta-analysis and review
  - Current WSA consensus is that there is insufficient evidence on the association of ETS exposure with asthma development in childhood

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WSA ETS (children) consensus (DRAFT -

Note: During the initial literature gathering for the meta-analysis mentioned above, we have observed indications of a specific source of publication bias where many studies measured ETS as one of their exposure parameters but either do not report data from ETS exposure per se, or do not present quantitative data where no association was observed.

Respiratory Effects: Lower Respiratory Illness (LRI)

- Diagnostic endpoints may include:
  - bronchitis, bronchiolitis, pneumonia
  - respiratory tract infections (e.g. respiratory syncitial virus - rsv)
- Diagnostic criteria may include:
  - parental report, hospitalisation, absenteeism, physician diagnosis

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Respiratory Effects: Lower Respiratory Illness

- Major reviewers covering this subject:
  - US Surgeon General - 1986
  - US EPA - 1992
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - SCOTH - 1998
  - WHO - 1999

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WSA ETS (children) consensus (DRAFT -

Respiratory Effects: Lower Respiratory Illness

- All 6 major reviews conclude a causal relationship between ETS exposure and childhood LRI (approx. 40 studies)
- General agreement
  - maternal smoking associated with a 1.5 to 2-fold increase in risk
  - weaker but significant association with paternal smoking
  - evidence of dose-response
  - little evidence of confounding
  - effect stronger in infants (< 2years)

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Respiratory illness:

"The most convincing epidemiological evidence relates to early lower respiratory infection in relation to postnatal exposure, yet we are lacking insights into how ETS increases the severity of these early (largely viral) infections."

Cook & Strachan, Thorax 1999; 54: 357-366

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Respiratory Effects: LRI - WSA Consensus

- WSA agrees that the epidemiological evidence for a causal association between parental smoking and LRI is consistent, particularly in infants
- there is currently insufficient evidence to determine the independent contributions of *in utero* and postnatal exposure
  - research is being pursued to further understand the relative contributions of ETS and *in utero* exposure
- at this time the epidemiological data support causal association between parental smoking and LRI, however:
  - underlying cause of LRI are infectious agents (bacteria, viruses)
  - defining the role of ETS in infection is an area which clearly requires more research
  - understanding of the mechanism is lacking
- until further research is completed no conclusion can be drawn on the causal role of ETS for LRI in children

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WSA ETS (children) consensus (DRAFT -

Currently WSA is performing an extensive literature analysis on all studies which investigate the association between ETS exposure during childhood and infections in general, including LRI. The objective of this review is to extract information on the mechanistic role of ETS in infection and identify research gaps which could provide information to clarify the associations.

Respiratory Effects: Respiratory Symptoms

- Diagnostic endpoints commonly include:
  - wheeze, cough, phlegm, breathlessness
- Diagnostic criteria:
  - virtually all based on questionnaires

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Respiratory Effects: Respiratory Symptoms

- Major reviews covering this subject:
  - US Surgeon General - 1986
  - US EPA - 1992
  - California EPA - 1997

  - *(SCOTH - 1998 and WHO - 1999 both included respiratory symptoms under their asthma review)*

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Respiratory Effects: Respiratory Symptoms

- All major reviews conclude a causal relationship between ETS exposure and respiratory symptoms in childhood
  - maternal smoking associated with an increase in risk (approximately 20%-100%)
  - association with paternal smoking generally weaker
  - association stronger in infants (< 2 years)

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WSA ETS (children) consensus (DRAFT - December 2002)

Respiratory Effects: Respiratory Symptoms

But note:

- inconsistent findings among studies for different symptoms
- interpretation of the data is particularly complicated by limitations in study design
- determination of defined diagnosis in infants is not easy!

Respiratory Effects: Symptoms - WSA Consensus

- WSA agrees that the evidence is consistent with respect to an association between ETS exposure in childhood and respiratory symptoms overall
- However there is no consistency with respect to any given symptom
- Investigations in other areas (asthma, and LRI) should help in understanding the role ETS plays in development of respiratory symptoms
- Currently we cannot draw any conclusions either on the causality of the association or on the impact of these associations with respect to general illnesses for the exposed child.

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Respiratory Effects: Lung Function Tests

- Diagnostic endpoints may include:
  - deficits in performance as measured by lung function tests (FEV, FVC etc..)

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Respiratory Effects: Lung Function Tests

- Major reviews covering this subject
  - US Surgeon General - 1986
  - US EPA - 1992
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - WHO - 1999

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Respiratory Effects: Lung Function Tests

- Approximately 35 studies reviewed in the 5 major reviews
- These reviews generally agree that:
  - parental smoking is associated with small (1-5%) deficits in lung function test (LFT) performance
  - cohort studies indicate a deficit in lung growth annually
  - these deficits are unlikely to be clinically significant but may contribute to development of more serious lung disease later in life (e.g. Chronic Obstructive Pulmonary Disease - COPD)
  - some residual effect from smoking during pregnancy is likely

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Respiratory Effects: Lung Function Tests - WSA Consensus

- in cross-sectional surveys parental smoking is associated with small (1-5%) deficits in LFT performance
- two cohort studies indicate a small deficit in lung growth annually, but the majority of studies do not
- these deficits are unlikely to be clinically significant but the contribution to development of more serious lung disease later in life (e.g. COPD) is currently unknown
- some residual effect from smoking during pregnancy is likely
- We have not concluded on causation because the results are so weak and the clinical significance uncertain that causation per se is irrelevant

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Respiratory Effects:
Bronchial Hyper-responsiveness (BHR)

- Measured as peak expiratory flow (PEF) after challenge (e.g. methacholine, histamine, exercise, cold air)
- Tests of BHR assess the underlying susceptibility of an individual to environmental stimuli
- BHR is also a characteristic symptom of asthma

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WSA ETS (children) consensus (DRAFT -

Respiratory Effects:
Bronchial Hyper-responsiveness (BHR)

- Major reviews covering this subject:
  - US Surgeon General - 1986
  - US EPA - 1992
  - Australian NH&MRC - 1997
  - SCOTH - 1998

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Respiratory Effects:
Bronchial Hyper-responsiveness (BHR)

- Relatively few studies published
- Earlier reviews, including a total of 6 studies (US SG, US EPA), suggested an effect was possible but inconclusive
- Later reviews, covering 10 and 14 studies respectively (NH&MRC, SCOTH), concluded that there was insufficient evidence
- Probability of publication bias suggested by SCOTH

Respiratory Effects:
BHR -
WSA Consensus

- WSA agrees that there does not appear to be clear support for a causal relationship between ETS exposure and bronchial hyper-responsiveness in children

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Otitis Media

- Diagnostic endpoints may include:
  - acute otitis media
  - recurrent otitis media
  - otitis media with effusion
  - persistent otitis media

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Note: Definitions from Thornton and Lee:

Acute Otitis media: is an inflammation of themiddle ear. It is usually preceded by a cold or other illness which leads to mucosal oedema and Eustachian tube blockage. It is characterised by earache and in most cases fever. The eardrum usually appears red and bulging. If the drum ruptures there will be discharge of pus from the ear, and this may be copious. The presence of fluid (I.e. pus) in the middle ear leads to conductive deafness.

Recurrent Otitis media: Usually regarded as three or more episodes of acute otitis media in 1 year.

Otitis media with effusion: is the term applied when fluid in the middle ear persists for some weeks or months following an attach of acute otitis media. It is characterised by an abnormal appearance of the eardurm, which may be coloured grey, yellow or blue, and mild to moderate conductive hearing loss, and is not associated with fe3ver. Otitis media with effusion may also be known as 'serous', 'secretory', or 'suppurative otitis media', 'middle ear effusion' or 'glue ear'.

Persistent Otitis media: In most cases of middle ear disease, the symptoms resolve in a short time, but sometimes the effusion may persist for several weeks or even months. If the condition lasts for 12 weeks or more, it may be defined as persistent otitis media. (also referred to as 'chronic otitis media with effusion, presistent middle ear effusion, and persistent secondary otitis media)

Otitis Media

- Major reviews covering this subject:
  - US Surgeon General - 1986
  - US EPA - 1992
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - SCOTH - 1998
  - WHO - 1999
- PM commissioned review:
  - Thornton & Lee - 1999

Otitis Media

- Earlier reviews based on relatively few studies:
  - US Surgeon General - 1986: 5 studies
  - US EPA - 1992: 15 studies
  - Australian NH&MRC - 1997: 19 studies
- These reviews indicated that results were not conclusive
- Later reviews based on around 40 studies

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WSA ETS (children) consensus (DRAFT -

Otitis Media: California EPA 1997

- 37 studies considered, odds ratios from 1.5-2.5
- Association strongest for infants under 2 years
- Several potential mechanisms proposed:
  - decreased mucociliary clearance
  - decreased eustachian tube patency
  - decreased patency due to ETS induced mucosal swelling
  - interaction between ETS exposure and increased viral upper respiratory tract infection
- Conclude the association is causal

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WSA ETS (children) consensus (DRAFT -

Otitis Media: SCOTH 1999

- 42 studies considered
- meta-analyses performed for either parent smoking and:
  - recurrent otitis media 1.48 (95% CI = 1.08-2.04) (7 studies)
  - middle ear effusion 1.38 (95% CI = 1.23-1.55) (4 studies)
  - referral for glue ear 1.21 (95% CI = 0.95-1.53) (7 studies)
- acute otitis media (no meta-analysis) - range 1.0 - 1.6 (8 studies)
- Conclude that the relationship is likely to be causal with "middle ear disease"

Otitis Media: WHO 1999

- chronic and acute otitis media
- around 40 studies, odds ratios around 1.2-1.4
  - association persists "virtually unchanged" after adjustment for potential biases
  - prognosis improved when children moved to smoke-free environment
  - biological mechanisms (unspecified) considered supportive
- based on the above concluded causal association

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WSA ETS (children) consensus (DRAFT -

Otitis Media: Thornton & Lee 1999

- Five categories of disease, 58 studies
  - postnatal ETS exposure associated with some classifications of OM, but not with others
  - Odds ratios typically below 1.5
- Note several "difficulties in interpreting data"....
  - separation of ETS exposure from maternal smoking during pregnancy
  - determining role of infection
  - inadequate control of potential confounding factors
- Therefore conclude that the evidence neither convincingly demonstrates nor excludes the possibility of a causal association between ETS exposure and middle ear disease

Thornton & Lee, Indoor & Built Environment, 1999; 8:21-39

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WSA ETS (children) consensus (DRAFT -

postnatal ETS exposure weakly associated with "recurrent OM", "OM with effusion" and "unspecified middle ear disease" but not with "acute OM" or "Persistent OM with effusion".

Otitis Media: WSA Consensus

- We agree that there is evidence of an association between parental smoking and "middle ear disease"
  - The epidemiology suggests a causal association for persistent OM and OM with effusion (odds ratios around 1.2-1.5)
  - The association is unclear for acute OM
- It is difficult to determine whether ETS or *in utero* exposure (or both) are playing a role
- the evidence would suggest a role in worsening an already present condition
  - Investigations in other areas (asthma, and LRI) should help in understanding the role of ETS in "middle ear disease"

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WSA ETS (children) consensus (DRAFT -

SIDS

- Diagnostic criteria
  - "The sudden death of an infant or young child which is unexpected by history and in which a thorough postmortem investigation fails to demonstrate an adequate cause of death."

2nd International conference on causes of sudden death in infants, Seattle, 1969.

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WSA ETS (children) consensus (DRAFT -

Note - Decision in 1996 to return to this definition - hence this definition was determined as being appropriate in 1996.

SIDS

- Major reviews covering this subject:
  - US EPA - 1992
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - SCOTH - 1998
  - WHO - 1999
- PM Commissioned review:
  - Sullivan & Barlow, Paediatric & Perinatal Epidemiology, 2001; 15: 144-200

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SIDS: US EPA - 1992

- Reviewed 8 studies - ORs ranged from 1.8 - 4.4
- Cannot differentiate the effects of prenatal from the effects of postnatal exposure
- Biological plausibility could not be assessed
- Causality could not be determined based on the information available

SIDS: California EPA 1997

- Postnatal ETS exposure
  - 10 studies reviewed
  - evidence for a postnatal effect fairly equivocal for most
  - causal association primarily based on two studies (Klonoff-Cohen et al, 1995; Blair et al, 1996)
  - importance of considering the impact of prenatal exposure on perceived postnatal effects noted

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WSA ETS (children) consensus (DRAFT -

SIDS: Australian NH&MRC - 1997

- Postnatal ETS exposure
  - 9 studies reviewed
  - risk increased by approximately 50% - 150% (RR of 1.5-2.5)
  - conclude that the available evidence supports a causal association between ETS exposure and SIDS
  - importance of considering the impact of prenatal exposure on perceived postnatal effects noted

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WSA ETS (children) consensus (DRAFT -

SIDS: SCOTH 1999

- marked reduction in OR after adjustment for confounding factors on SIDS studies
  - maternal smoking in pregnancy
    - crude OR **2.77** (2.45-3.13; n=34) adj OR **2.08** (1.82-2.38; n=19)
  - postnatal maternal smoking
    - crude OR **3.10** (2.70 - 3.56; n=9) adj OR **1.94** (1.55 - 2.43; n=4)
- studies where mother smoked only postnatally, or where father and others smoked strongly support a postnatal effect
- conclude a causal association between maternal smoking and SIDS, and that postnatal exposure may be the more important factor.

Anderson & Cook. Thorax. 1997; 52: 1003-1009

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WSA ETS (children) consensus (DRAFT -

Note: ORs taken from table 2, Anderson and Cook, 1997.

For prenatal effects took random effects method meta-analyses results for all studies and for those with adjusted Ors.

For the postnatal studies the fixed effects comparison was taken because there were not sufficient studies for the random effects.

Note the large impact of adjustment in these studies.....

SIDS: WHO 1999

- Analysis based on Bradford Hill "Aspects"
- Maternal Smoking associated with an increased risk:
  - 3-fold increase prior to prone sleeping customs changed (RR ~ 3)
  - 5-fold increase subsequent to declines in prone sleeping (RR ~ 5)
- Most of the association appears to be with *in utero* exposure rather than postnatal exposure
- A weaker association with postnatal exposure
  - OR 1.38 for paternal smoking; noted that this is quite possibly due to confounding by other factors

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WSA ETS (children) consensus (DRAFT -

Synthesis report: "The literature is limited potentially by uncertainty as to the underlying mechanisms by which ETS might cause SIDS and the relevant confounding factors. Nonetheless, clear evidence exists that maternal smoking is associated with increased risk for SIDS, although the comparative contributions to the risk of prenatal and postnatal exposure cannot be readily separated. The evidence does not indicate a strong effect of smoking by the father or of other persons in the household.

SIDS: Sullivan & Barlow 2001

- Majority of evidence suggests that maternal smoking is an important independent risk factor for SIDS
- Majority of the effect appears to be explained by prenatal exposure
- Limited evidence that postnatal exposure is associated with further increases in risk

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WSA ETS (children) consensus (DRAFT -

SIDS: Prenatal vs Postnatal

- Many reviewers conclude that maternal prenatal smoking is more important although postnatal maternal smoking has an independent influence (e.g. WHO, California-EPA)

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WSA ETS (children) consensus (DRAFT -

SIDS: Prenatal

"Overall the majority of the evidence suggests that maternal smoking is an important independent risk factor with a causal biological link to SIDS, ... Although the effects of pre- and post-natal smoke exposure are difficult to separate, the majority of the effects of smoking can be explained by prenatal smoking by the mother. The limited evidence of a further increase from environmental tobacco smoke, such as that associated with smoking in the same room as the infant, and the presence of other smokers in the household is less well established."

Sullivan and Barlow, Paediatric & Perinatal Epidemiology, 2001; 15: 144-200

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SIDS:
Prenatal vs Postnatal

- SCOTH (Anderson & Cook) suggest the postnatal exposure is more important, the effect of prenatal exposure acting as a surrogate for postnatal exposure

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WSA ETS (children) consensus (DRAFT -

SIDS: Postnatal

"We conclude that the epidemiological evidence points to a causal relationship between SIDS and postnatal exposure to tobacco smoke. A large part of the association with prenatal exposure is potentially explicable as a postnatal effect. Whether prenatal exposure has an effect independent of postnatal exposure (apart from through effects of birthweight) remains to be determined, but for public health purposes there is a clear indication that both prenatal and postnatal exposure should be avoided."

Anderson & Cook. Thorax. 1997; 52: 1003-1009

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WSA ETS (children) consensus (DRAFT -

SIDS:
WSA Consensus

- We agree that maternal smoking is associated with an increased incidence of SIDS (reported odds ratios of between 2 and 5)
- Difficulties in separating out effects of prenatal and postnatal exposure
- Most reviewers, who have attempted to separate out the effects, have concluded that prenatal exposure is more important
- At this time the WSA consensus is that exposure *in utero* is causally related to SIDS
- There is currently insufficient evidence with respect to the nature of the association with postnatal exposure

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WSA ETS (children) consensus (DRAFT -

Note: The group is aware of a number of publications which discuss a potential mechanism involving the sleep apnoea response. This has not been fully reviewed at this time. We note the need to look at this more closely and perform a fuller analysis of these studies.

Childhood Cancer:

- Investigations into the association between ETS exposure in childhood and almost all types of childhood cancer have been reported

Childhood Cancer

- Major reviews covering this subject:
  - US Surgeon General - 1986
  - California EPA - 1997
  - Australian NH&MRC - 1997
  - WHO - 1999
- PM commissioned review
  - Thornton & Lee, Indoor & Built Environment, 1998; 7: 65-86

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WSA ETS (children) consensus (DRAFT -

Note: It is of interest to note that most of these reviews have covered the same studies in their review. This is probably a reflection of the clarity of diagnostic criteria for these diseases in comparison to the respiratory diseases etc.. discussed above. This is noteworthy because it suggests a fairly complete review of all the information, whereas it was striking for other endpoints, although many of the studies were in common there is a considerable variation in the studies selected for review by each body.

Childhood Cancer: US Surgeon General - 1986

- The potential for an association between parental smoking and cancer reviewed:
  - "overall cancer risk" in only 2 studies
  - specific cancers in 6 studies
- The report concluded that the evidence for parental smoking and childhood cancer was not clear

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WSA ETS (children) consensus (DRAFT -

Childhood Cancer: California-EPA - 1997

- reviewed a number of studies on all cancers, leukemia, lymphoma and non-Hodgkins lymphoma and other rare childhood cancers
  - 7 studies reviewed, including pre-natal, postnatal and pre-conception exposures
- conclude that evidence was generally inadequate to draw any firm conclusions

Childhood Cancer: Australian NH&MRC

- Reviewed 9 studies, and 2 reviews
- Conclude evidence for an association between "passive smoking" and childhood cancer is weak

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Childhood Cancer: Thornton & Lee - 1998

- reviewed 58 studies
- a weak association between childhood cancer and maternal smoking prior to pregnancy was observed
- evidence for paternal smoking and various other sources slightly stronger
- evidence for maternal smoking during and after pregnancy unconvincing
- evidence inadequate to draw a conclusion of a causal association

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Childhood Cancer: WHO - 1999

- Meta-analyses - maternal smoking during pregnancy:
  - all neoplasms RR=1.11 (95%CI 1.00-1.23; n=11)
  - all leukemias RR=1.14 (95%CI 0.97-1.33, n=4)
  - acute lymphoblastic leukemia RR=1.14 (95%CI 0.84-1.54, n=5)
  - CNS RR=1.04 (95%CI 0.93-1.18,n=12)
  - all lymphatic and hematopoietic RR=1.03 (95%CI 0.9-1.17,n=9)
  - non-Hodgkins or all lymphoma RR=1.13 (95%CI 0.85-1.49,n=6)
  - neuroblastoma RR=1.25 (95%CI 0.75-2.00, n=3)
  - kidney or Wilms tumour, RR=0.95 (95%CI 0.78-1.19, n=5)
- Meta-analysis - paternal smoking during pregnancy
  - brain tumours, RR=1.22 (95%CI 1.05-1.40, n=10)
  - non-Hodgkins lymphomas, RR=2.08 (95%CI 1.08-3.91,n=4)

Bofetta et al, WHO consultation, 1999

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WSA ETS (children) consensus (DRAFT -

Childhood Cancer: WHO - 1999

- Comment that exposure could act either before, during or after pregnancy
- Requires further research

- Conclude a causal association cannot be confirmed
  - effects generally too small
  - possibility of confounding high

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WSA ETS (children) consensus (DRAFT -

Note: Samet's synthesis differs in the conclusion in that he states "In conclusion, there is suggestive evidence linking exposure to tobacco smoke and childhood cancer."

Childhood Cancer: WSA Consensus

- Little, if any, evidence for an association with postnatal exposure
- General agreement from reviewers that biases and confounding could account for much of the associations observed
- Based on current available evidence there is no causal association between postnatal ETS exposure and childhood cancer

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WSA ETS (children) consensus (DRAFT -

Note: There has been much discussion regarding prenatal or preconceptual exposure in this context as well. Our conclusions are that the evidence is much the same as that for postnatal exposure.

Neurodevelopment / Behaviour

- Major reviews covering this subject
  - California EPA - 1997
  - WHO - 1999

Neurodevelopment / Behaviour California -EPA 1997

- most of the discussion is on *in utero* effects
- 6 out of 7 studies reviewed on postnatal ETS exposure reported some weak effects on cognition or behaviour
- potential for bias and confounding noted to be high
- conclude data suggestive of an association but there was insufficient data to conclude that there was a causal association

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WSA ETS (children) consensus (DRAFT -

Neurodevelopment / Behaviour WHO - 1999

- 9 of 17 studies reviewed report some association for postnatal ETS exposure and some measure of neurodevelopment
- note problems in interpretation, including accounting for potential confounders and particularly in separating out the effects of prenatal exposure
- one animal study was cited to indicate changes in the development of the hindbrain
- conclude that effects are plausible but not yet established

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WSA ETS (children) consensus (DRAFT -

Animal study cited = Gospe, S M, Zhou, W.W. and Pinkerton, K.E. "Effects of environmental tobacco smoke exposure in utero and/or postnatally on brain development." Pediatr res., 1996; 39(3): 494-8

"Perhaps the strongest evidence for a causal relationship between ETS exposure and adverse effects on neurodevelopment is from a single animal study. Gospe et al. exposed pregnant rat dams to sidestream smoke (SS) or filtered air (FA) for 4 hours a day, everyday throughout gestation, and exposed the offspring to either SS or FA for nine weeks postnatally for a total of 4 different exposure conditions: *in utero* FA-postnatal FA, *in utero FA - postnatal SS, in utero SS - postnatal FA, and in utero SS - postnatal SS.* After 9 weeks of postnatal exposure, the animals were sacrificed and the brains were divided into forebrain and hindbrain, analyzed for DNA, protein, and cholesterol concentration. Two-way analysis of variance indicated that postnatal SS reduced by 4% hindbrain DNA concentration, an indicator of cellular density, and increased by 8.9% the hindbrain protein/DNA ratio, an index of cell size, although the total hindbrain weight was no different. *In utero* exposure to SS had no effect. This study provides the first clear biologic evidence for an alteration of brain development due to postnatal but no prenatal ETS exposure."

Extract taken from Eskenazi & Castorino WHO consultation document, p 13-14 - with reference to the study by Gospe et al, 1996 (full reference above)

Note the WHO summary conclusions seem less strong than those of Eskenazi and Castorino

Neurodevelopment / Behaviour WSA Consensus

- A number of studies suggest that children exposed to ETS postnatally may exhibit small neuro-developmental deficits as measured by:
  - academic achievement, cognitive skills, hyperactivity or attention deficit disorder, criminal behaviour
- Interpreting these studies is generally acknowledged by various reviewers as being difficult because
  - identification of subjective measures of effects is difficult
  - potential for bias and confounding is enormous
- Current epidemiological data are not sufficient to support a causal association
- Animal data is, to-date, unconvincing
- Future research in animal studies could help to clarify these relationships

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WSA ETS (children) consensus (DRAFT -

Childhood Infections: General comments

- A number of papers discuss the potential role of ETS exposure in increasing childhood susceptibility to infections, including:
  - meningitis
  - *Helicobacter pylori*
  - respiratory infections in general

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WSA ETS (children) consensus (DRAFT -

Childhood infections: General Comments

- A role for ETS exposure in childhood infections has been suggested, (e.g. as an adjuvant acting similarly to air pollution)
- If such a role is played by ETS in childhood infections, this could also contribute to some of the associations noted in other areas:
  - otitis media, leukemia, SIDS and respiratory disease
- PM is currently investigating the totality of the evidence on ETS and childhood infections, including LRI, in order to possibly design studies which would provide mechanistic information

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WSA ETS (children) consensus (DRAFT -

Re Adjuvant - see L.F.A DeSwert, Eur J. Pediatr 1999. 158:89-94

Childhood Infections: WSA Consensus

- The epidemiological evidence suggests an association
- There is insufficient information available to draw any firm conclusions on the role of ETS exposure on childhood infections.
- PM's current project on analysis of the available literature is primarily aimed at identifying further research directions which could help to provide mechanistic information

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WSA ETS (children) consensus (DRAFT -

Miscellaneous Effects

Note: Many other potentially detrimental effects of ETS exposure on children have been reported to various degrees. Some of these are listed below, although they have not been reviewed here:

dental decay

cardiovascular disease

anesthetic recovery

appendicitis

allergic sensitisation

thyroid function

gastrointestinal / oesophageal effects

WSA consensus summary

- Based on current available evidence WSA consensus finds:
  - Sufficient evidence for a causal relationships for ETS exposure in childhood and:
    - asthma exacerbation
  - Epidemiological evidence supportive of a causal relationship, insufficient evidence on potential mechanisms for ETS exposure in childhood and:
    - respiratory symptoms
    - lung function deficits
    - lower respiratory infections
    - Childhood infections
    - otitis media
  - Insufficient information to conclude causality for ETS exposure in childhood and:
    - neuro-developmental effects
    - lung function growth
    - asthma development
    - SIDS
  - a causal relationship between ETS exposure in childhood is unlikely for:
    - childhood cancers
    - bronchial-hyperresponsiveness

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WSA ETS (children) consensus (DRAFT - December 2002)

Further work

- Full meta-analysis of studies on ETS in childhood and Asthma development
- Analysis of the literature on the role of ETS in infections to identify future studies which may provide information regarding mechanisms for infections, symptoms, asthma and lung function effects
- Further analysis of the potential role of the apnoeic response in SIDS
- Investigations into potential animal models to elucidate the potential role of ETS exposure on neurodevelopmental / behavioural effects
- In addition, many of the inconsistencies observed in the literature may be due to the presence of susceptible populations. Further investigations into such sources of susceptibility may also help to clarify the causal nature of the associations observed in these cases